REMARKS

Reconsideration of the application is respectfully requested. Claims 30-47 are pending.

I. Amendment to the Title

The Title has been amended to correspond more closely to the claimed subject matter.

II. Amendment to the Drawings

The drawings submitted 2/14/00 (Figs. 6A-6B) are hereby canceled in favor of new Figs. 6A-6B, discussed further below.

III. Objection to Figures 6A-6B Under 35 USC 132

The drawing sheet submitted February 11, 2000 (Figs. 6A-6B) was objected to as allegedly being new matter. Those figures had been submitted in response to an objection under 37 CFR 1.83(a) for not showing "every feature of the invention specified in the claims" (Office action dated August 11, 1999). The objection is believed to be moot in light of new Figs. 6A-6B enclosed herewith.

A new drawing can be added by amendment provided that it does not introduce new matter (35 USC 132). There is no new matter if the added subject matter is supported by the original disclosure in accordance with the first paragraph of 35 USC 112, that is, if the original disclosure conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, the applicant was in possession of the invention (e.g., Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 19 USPQ2d 1111, Fed. Cir. 1991).

According to 37 CFR 1.83(a), "The drawing in a nonprovisional application must show every feature of the invention specified in the claims. However, conventional features disclosed in the description and claims, where their detailed illustration is not essential for a proper understanding of the invention, should be illustrated in the drawing in the form of a graphical drawing symbol or a labeled representation (e.g., a labeled rectangular box)." Furthermore, only details of "sufficient importance" need be shown (see MPEP 608.02(d)).

Pending claim 30 recites: "An instrument for monitoring a nucleic acid amplification reaction over multiple thermal cycles, comprising:

(a) a thermal cycler capable of alternately heating and cooling, and adapted to receive, a reaction vessel containing an amplification reaction mixture comprising a target nucleic acid, reagents for nucleic acid amplification, and a detectable nucleic acid binding agent, in a sealed vessel condition; and

(b) an optical system including a detector operable to detect an optical signal related to the amount of amplified nucleic acid in the reaction vessel over a multiple-cycle period, with the reaction vessel in a sealed condition, allowing determination of a cycle-dependent change in such optical signal over a multiple-cycle period with the reaction vessel in its sealed condition.

Consistent with claim 31, new Fig. 6A shows an instrument comprising (a) a thermal cycler adapted to receive a reaction vessel for containing an amplification reaction mixture comprising a target nucleic acid, reagents for nucleic acid amplification, and a detectable nucleic acid binding agent, in a sealed vessel condition, and (b) an optical system including a detector operable to detect an optical signal related to the amount of amplified nucleic acid in the reaction vessel over a multiple-cycle period, with the reaction vessel in a sealed condition, allowing determination of a cycle-dependent change in such optical signal over a multiple-cycle period with the reaction vessel in its sealed condition. With reference to dependent claim 32, new Fig. 6B shows a like instrument adapted to operate with a plurality of such reaction vessels.

Support for new Figs. 6A-6B can be found, for example, in the specification at page 13 line 27 through page 15 line 13 and Example VIII (pages 28-30). For example, on page 14, beginning at line 10, reference is made to a thermocycler (also known as a thermal cycler) which contains a heat block capable of carrying out 48 amplification reactions simultaneously, as was available at the time of the invention from Perkin-Elmer Cetus Instruments. With reference to the excerpt from the Perkin Elmer Cetus catalog (Summer, 1990) provided with applicants' response on June 27, 2001, page 11 notes that the cited cycler was "microprocessor-controlled", to implement a user-selected cycling profile. This is demonstrated in Example VIII, wherein such a thermocycler was used to automatically cycle between 94°C and 50°C for 1 minute each, for 30 cycles.

The presently claimed invention also includes an optical system that can be used to determine a cycle-dependent change in an optical signal from an amplification reaction over a multiple-cycle period, while the reaction vessel remains in a sealed (unopened) condition (e.g., page 14 lines 12-16).

In one embodiment, fiber optic leads can be placed in proximity to each of one or more reaction vessels, so that an optical signal can be transmitted from each reaction mixture to a detector. Such a fiber optic lead can be positioned in proximity to a reaction mixture, without an intervening vessel wall, as noted at page 14, lines 26-28.

According to another embodiment, each reaction vessel can have a clear or translucent portion (e.g., cap) through which an optical signal can be collected. In yet another embodiment, the specification notes that an optic fiber is not required where a detector and thermocycler are housed together, rather than independently (see page 14 lines 31-34, for example). Example VIII refers to an optical detection system that included a Spex-Fluorolog-2 fluorometer equipped with a fiber optic accessory and standard data collection software (see page 28 lines 28-30). Other detection formats are also discussed, such as a microtiter format (page 14 line 35 et seq.) and detection by optical density-based methods and light scattering (page 15, lines 7-25).

In view of the foregoing remarks, it is respectfully submitted that enclosed Figs. 6A-6B are fully supported by the application as originally filed and therefore do not add new matter. Withdrawal of the objection is respectfully requested.

IV. Obviousness Rejection Under 35 U.S.C. 103(a)

Claims 30-47 were rejected over Haff et al. (Amplifications 1:8-10, 1989) in view of Mackay (EP 266881) and newly cited Schnipelsky et al. (US 5,229,297). Schnipelsky et al. was characterized as disclosing a method and apparatus for monitoring PCR reactions in a "closed cuvette ... such that detection reagents can be provided without exposing the reaction contents to the atmosphere, and for enabling on-line analysis" (Office action at page 3). The Examiner contends that it would have been obvious to combine the teachings of Schnipelsky et al. with Haff and Mackay to arrive at the presently claimed invention.

The Examiner stated further that the Declaration filed under 37 CFR 1.132 filed 7/27/01 was "insufficient" on the theory that Schnipelsky et al. "establishes that it was known to provide a cuvette for containing detection reagents associated with a PCR reaction mixture in a closed vessel such that the reagents can be provided for analysis without interfering with the reaction and without the necessity of removing reaction products from the cuvette" (Office action at page 4). The rejection is respectfully traversed.

The PTO has the burden of establishing *prima facie* obviousness, and can meet this burden "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references" In re Fine, 837 F.2d 1071, 5 USPQd2 1596 (Fed. Cir. 1988).

Haff et al. teaches away from the present invention. Haff et al. teaches running replicates of a reaction mixture to allow different aliquots to be removed after different numbers of cycles. This approach is susceptible to the risk of variability among different replicates and clearly is less desirable than conducting all measurements on a single reaction mixture in a sealed condition. Haff et al. also failed to recognize that an indicator reagent could be included in a nucleic acid reaction mixture to allow amplification to be measured over multiple cycles without opening the reaction vessel.

Furthermore, although Haff et al. mentions the possibility of automating their method (see page 9 under "Instrumentation"), the cited device (a Perkin-Elmer Model LS-2B spectrophotometer with an autosampler) would only have automated the transfer of each assay mixture (the result of mixing an aliquot of a PCR reaction mixture with dye solution and TE buffer) from an autosampling tray into and out of the fluorescence cuvette for fluorescence measurement. The cited autosampler had no capacity to automate the collection of aliquots from the PCR reactions, nor mixing of those aliquots with dye solution, so these steps would still need to be done by the user.

Nor are the deficiencies of the Haff et al. remedied by Mackay. Mackay teaches an apparatus for measuring sample components using fibre optics (see Abstract). Temperature control is not discussed. There is no suggestion of utilizing a thermal cycler capable of iteratively heating and cooling a sample to promote amplification of target nucleic acids, nor of detecting an increase in signal over multiple cycles while the reaction vessel remains in a sealed condition, nor how such detection could be accomplished.

Nor are those deficiencies remedied by newly cited Schnipelsky et al. Schnipelsky et al. discloses a device, referred to in the patent as a "containment cuvette", for PCR amplification and detection. The device includes numerous compartments that contain various liquids, such as a sample solution, detection reagents, and wash solutions. These liquids are transferred in a particular order to a reaction compartment, depending on the stage of the PCR protocol. For example, in Figs. 1-7, the device is configured as a flat pouch in which a series of compartments are located along the

path of a roller. Movement of the roller across the compartments, one-by-one, causes transfer of the contents of each compartment to a reaction region. In another embodiment, transfer of different liquids is accomplished using compartments equipped with pistons (Figs. 8-19).

There is no suggestion in Schnipelsky et al. of performing nucleic acid amplification in accordance with the present invention using an instrument comprising a thermal cycler in conjunction with an optical system including a detector operable to detect an optical signal related to the amount of amplified nucleic acid in the reaction vessel over a multiple-cycle period, with the reaction vessel in a sealed condition, allowing determination of a cycle-dependent change in such optical signal over a multiple-cycle period with the reaction vessel in its sealed condition.

Rather, detection is not performed until after amplification is complete, at which time (1) the amplified material is transferred from the reaction compartment to a separate detection site, (2) a detection material is also transferred from its own compartment to the detection site, and (3) the amplified material is then detected (for example, see column 3 lines 49-57). Alternatively, the detection material may already be present in the detection site, but the amplification reaction mixture still must be transferred to the detection site too (see column 6 line 44 to column 7 line 67). There is no suggestion in Schnipelsky et al. (1) of performing amplification with a detection material being present in the reaction mixture, (2) that amplification could be monitored over multiple cycles while the reaction mixture remains in a sealed condition, or (3) what detection could be used to accomplish such monitoring. In fact, such monitoring would be impossible since Schnipelsky et al. detection material is not added to the reaction mixture until after amplification is complete.

In conclusion, there is nothing in the cited references that would have suggested to one of ordinary skill in the art to arrive at the present invention. Since the cited references fail to suggest that the claimed invention should be made, withdrawal of the rejection is respectfully requested.

V. Obviousness-Type Double Patenting Rejection

The claims were rejected for alleged obviousness-type double patenting over claims in copending application Ser. No. 08/266,061. However, that application is abandoned. Accordingly, withdrawal of the rejection is respectfully requested.